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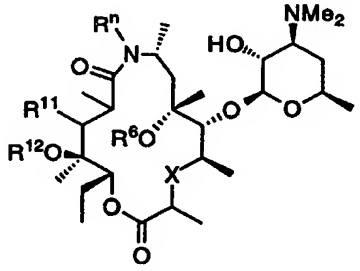
(54) Title: 8A–AZALIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT



(I)

(57) Abstract

Compounds are disclosed which are represented by formula (I) as well as salts and hydrates thereof wherein in part: X represents CH_2, CHF, CF_2, $C{=}CH_2$, CHSR, $CHCH_3$, C=S, C=O or CHOR. Pharmaceutical compositions and methods of treatment are also included.

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TITLE OF THE INVENTION

8A-AZALIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT

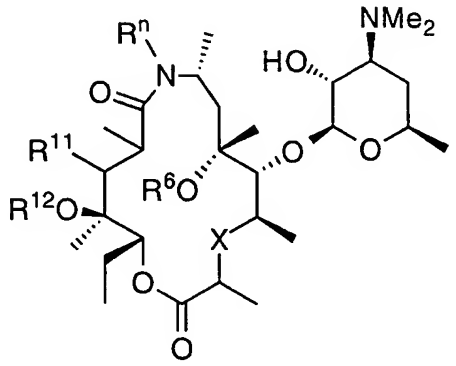
BACKGROUND OF THE INVENTION

The present invention relates to 8a-azalides, compositions containing such compounds and methods of use therefore. Azalides are structurally similar to erythromycin A, with the exception of the presence of a ring nitrogen atom at the 8a-position. The compounds of the present invention are further distinguished from erythromycins and erythromycin-like compounds in that the cladinose moiety has been cleaved from the molecule.

The 8a-azalides of the present invention are potent antibiotics which are useful for the treatment of gram positive and gram negative organisms. As such the compounds find utility in human and veterinary medicine for the treatment of infections caused by susceptible organisms.

SUMMARY OF THE INVENTION

The present invention addresses a compound represented by formula I:



I

or a salt or hydrate thereof wherein:

X represents CH_2, CHF, CF_2, $C=CH_2$, CHSR, $CHCH_3$, C=S, C=O, C=NOR, CHNR'R" or CHOR;

R represents H, C_{1-6} alkyl, CS_2CH_3 or phenyl, said C_{1-6} alkyl being uninterrupted or interrupted by O, $S(O)_y$ wherein y is 0, 1 or 2, NH or C(O), and being unsubstituted or substituted with 1-3 R^a groups, as defined below;

R^n represents H, C_{1-6} alkyl or $-(CH_2)_nAr$ wherein n represents an integer of from 1 to 10, said C_{1-6} alkyl chain and $-(CH_2)_n$ being uninterrupted or interrupted by 1-3 of O, $S(O)_y$, NH, NCH_3 or C(O) wherein y is as previously defined, and being unsubstituted or substituted with 1-3 R^a groups as defined below,

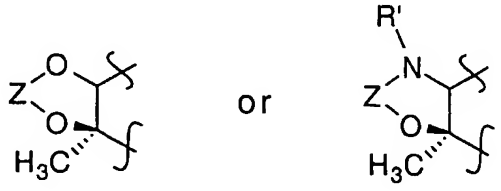
or R^n is taken in conjunction with R^6 as defined below;

Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 groups R^a which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, phenyl and pyridyl and when two substituent groups are attached to Ar, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, containing from 0-2 heteroatoms as defined above;

R^{11} is selected from the group consisting of: OH, NR'R", $O(CH_2)_nAr$ and $S(CH_2)_nAr$, wherein $(CH_2)_n$ and Ar are as previously defined;

R^{12} is selected from the group consisting of: H, C_{1-6} alkyl and $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as previously defined;

or R^{11} and R^{12} taken together with the intervening atoms form an additional ring of the following structure:



wherein :

R' is selected from H, C_{1-3} alkyl, NHR"and $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as previously defined;

R" represents H, C_{1-3} alkyl or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined above;

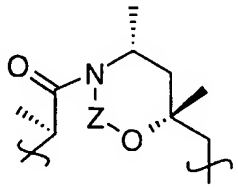
Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 wherein R" and X are as defined above;

R^z represents C_{1-6} alkyl or phenyl;

R^6 represents H or CH_3; and

R^n is as defined above; or

R^6 and R^n taken together with the intervening atoms form the following structure:



in which Z is as described above.

Also included is a pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

Also included is a method of treating a bacterial infection in a mammalian patient in need of such treatment which is comprised of administering to said patient a compound of formula I in an amount which is effective for treating a bacterial infection.

DETAILED DESCRIPTION OF THE INVENTION

The invention is described in connection with the following definitions unless otherwise specified.

Alkyl as used herein refers to C_{1-6} straight or branched chain alkyl groups which are uninterrupted or interrupted by 1-3 of N, O, $S(O)_y$, wherein y is 0, 1 or 2, or C=O as specified, and which are unsubstituted or substituted with from 1-3 R^a groups. When interrupted, a methylene spacer can be present which is adjacent to an interrupting moiety. Thus, this would include, for example, $-CH_2-O-$ and $-O-CH_2-$. When two or three of these moieties are present, they may be separate or together. Me represents methyl.

Each R^a is selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, phenyl and pyridyl and when two substituent groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, containing from 0-2 heteroatoms as defined above.

Acyl refers to C_{1-5} alkyl-C(O)-.

When the group $-(CH_2)_nAr$ is present, the alkyl portion $-(CH_2)_n$ is uninterrupted or interrupted as described above, with 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O), and is unsubstituted or substituted with 1-3 R^a groups. This includes groups where the interrupting atom is at either end of the chain. Thus, -C(O)-phenyl, -NH-phenyl, $-C(O)NH-(CH_2)_{1-10}$-phenyl, $-CH_2-O-$phenyl as well as like groups are included. More than one interrupting moiety can be present, separate or together. Thus, $-OC(O)-$, $-S(O)_yNH-$, -C(O)NH- and similar groups are included, as well as polyethers, polythioethers and the like.

Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 groups selected from R^a which is halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, phenyl and pyridyl and when two R^a substituent groups are attached to Ar, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered aromatic or non-

aromatic ring. Examples include phenyl, naphthyl, quinolinyl, isoquinolinyl, pyridyl, imidazolyl, pyrrolyl, thiophenyl, benzothiazolyl, thiazolyl, furanyl, benzofuranyl, naphthosultamyl, dibenzofuranyl, fluorenonyl, phenanthrenyl and indolyl.

Halo means Cl, F, Br or I.

A preferred aspect of the invention relates to compounds of formula I wherein X contained in the azalide ring represents CH_2, CHF, or CF_2. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds of formula I wherein X contained in the azalide ring represents $C{=}CH_2$, C=S or CHSR. Within this subset of compounds, all other variables are as originally defined.

Yet another preferred aspect of the invention relates to compounds of formula I wherein X contained in the azalide ring represents C(O) or CHOR. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^n represents H, $C_{1\text{-}6}$ alkyl or $(CH_2)_nAr$. Within this subset of compounds all other variables are as originally defined.

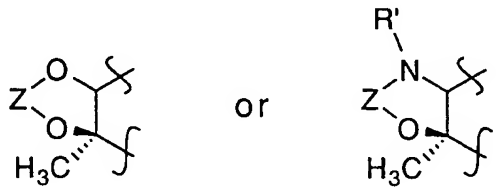
Another preferred aspect of the invention relates to compounds wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and $C_{1\text{-}3}$ alkyl. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^{12} represents H, $C_{1\text{-}6}$ alkyl or $(CH_2)_n$-Ar.

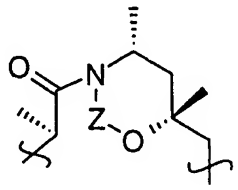
Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring of the following structure:



wherein Z represents CH_2, C(O), C(NR"), P(O)OR", $P(O)NR^nR"$, $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 wherein R', R" and X are as originally defined. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^6 and R^n taken together with the intervening atoms form the following structure:



in which Z is as described above. Within this subset all other variables are as originally defined.

A preferred aspect of the invention relates to compounds of formula I wherein:

X contained in the azalide ring represents CH_2, CHF or CF_2;

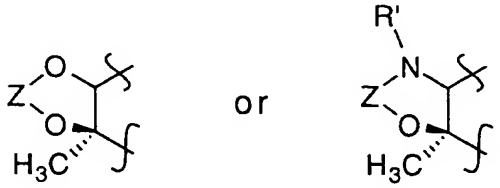
R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$,

wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl, phenyl and pyridyl or R^n is taken in conjunction with R^6 as defined below;

R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined;

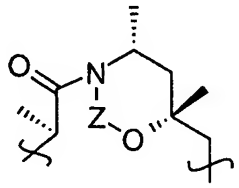
R^{12} represents H, C_{1-6} alkyl or $(CH_2)_n$-Ar;.

or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring of the following structure:



wherein Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined;

R^6 is H or CH_3, or R^6 and R^n taken together with the intervening atoms form the following structure:



in which Z is as described above.

Another preferred aspect of the invention relates to compounds of formula I wherein:

X contained in the azalide ring represents $C=CH_2$, C=S or CHSR;

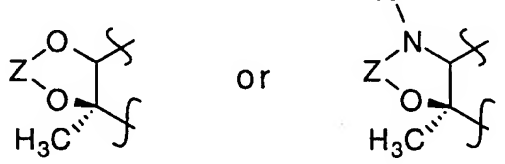
R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$,

wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl, phenyl and pyridyl or R^n is taken in conjunction with R^6 as defined below;

R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined;

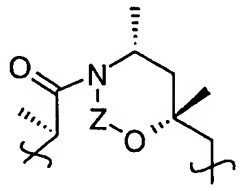
R^{12} represents H, C_{1-6} alkyl or $(CH_2)_n$-Ar;.

or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring of the following structure:



wherein Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 wherein R', R" and X are as originally defined;

R^6 is H or CH_3, or R^6 and R^n taken together with the intervening atoms form the following structure:



in which Z is as described above.

Another preferred aspect of the invention relates to compounds of formula I wherein:

X contained in the azalide ring represents C(O) or CHOR;

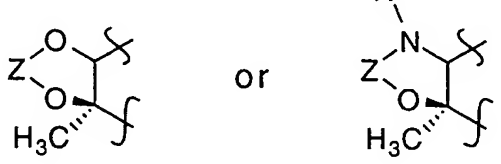
R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$,

wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl, phenyl and pyridyl or R^n is taken in conjunction with R^6 as defined below;

R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined;

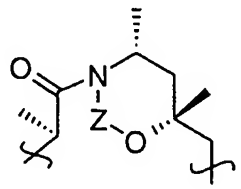
R^{12} represents H, C_{1-6} alkyl or $(CH_2)_n$-Ar;.

or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring of the following structure:



wherein Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 wherein R', R" and X are as originally defined;

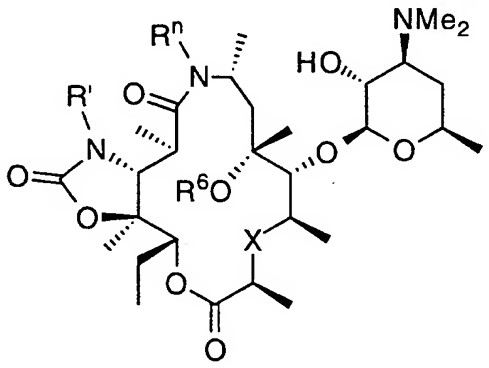
R^6 is H or CH_3, or R^6 and R^n taken together with the intervening atoms form the following structure:

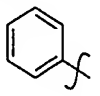
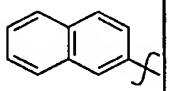
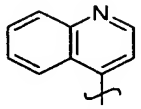
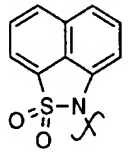
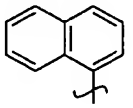
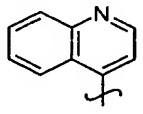


in which Z is as described above.

Specific compounds which are included in the present invention are set forth below.

Table 1



#	X	R^n	R^6	R'	Ar
1	CH_2	CH_3	H	$(CH_2)_4Ar$	
2	CH_2	CH_3	H	$(CH_2)_4Ar$	
3	CH_2	CH_3	H	$(CH_2)_4Ar$	
4	CH_2	CH_3	H	$(CH_2)_3Ar$	
5	CHF	CH_3	CH_3	$(CH_2)_4Ar$	
6	CF_2	CH_3	CH_3	$(CH_2)_4Ar$	

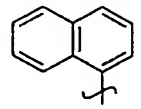
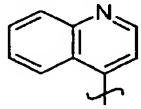
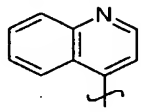
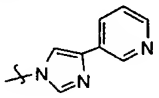
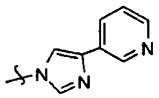
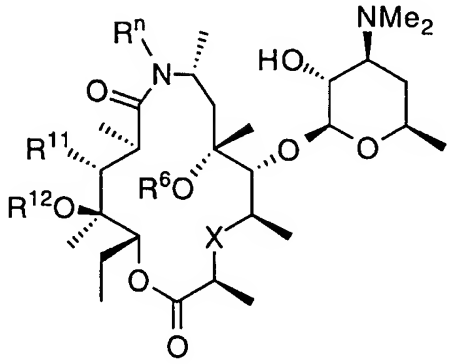
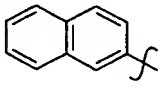
7	CH_2	---CH_2---		$(CH_2)_4Ar$	
8	CH_2	---CH_2---		$NH(CH_2)_3Ar$	
9	C=O	CH_3	CH_3	$NH(CH_2)_3Ar$	
10	C=O	H	CH_3	$(CH_2)_4Ar$	
11	C=O	CH_3	CH_3	$(CH_2)_4Ar$	

Table 2



#	X	Rn	R6	R11	R12	Ar
10	CH_2	CH_3	H	$O(CH_2)_3Ar$	H	
11	CH_2	CH_3	H	OH	$(CH_2)_3Ar$	

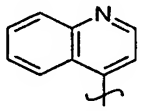
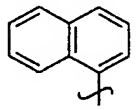
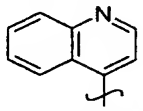
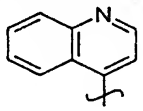
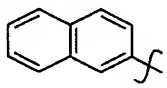
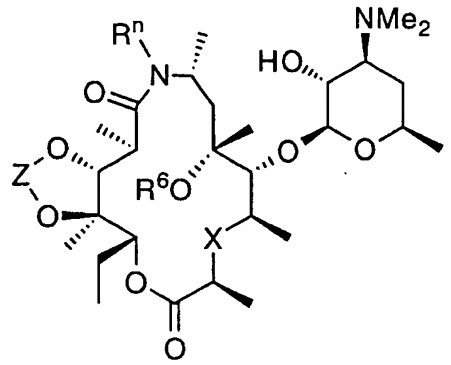
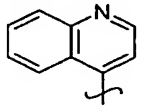
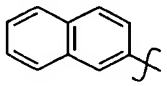
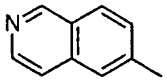
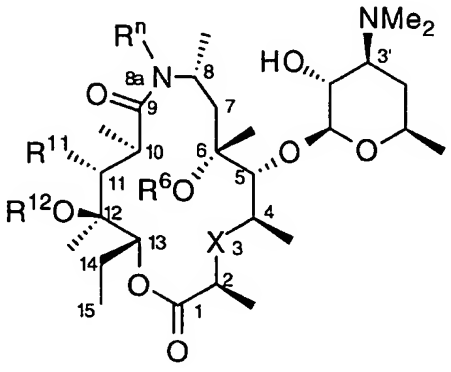
12	CH_2	CH_3	H	$O(CH_2)_3Ar$	H	
13	CHF	CH_3	CH_3	$O(CH_2)_4Ar$	H	
14	CH_2	CH_3	H	$S(CH_2)_4Ar$	H	
15	CH_2	$(CH_2)_4Ar$	H	OH	H	
16	CH_2	$(CH_2)_4SO_2Ar$	H	OH	H	
17	C=O	CH_3	CH_3	OH	H	------
18	CH_2	--$P(O)OCH_3$--		OH	H	------
19	C=O	--$P(O)OCH_3$--		OH	H	------
20	CH_2	--$C(O)CH_2$--		OH	H	------
21	C=O	--$C(O)CH_2$--		OH	H	------

Table 3



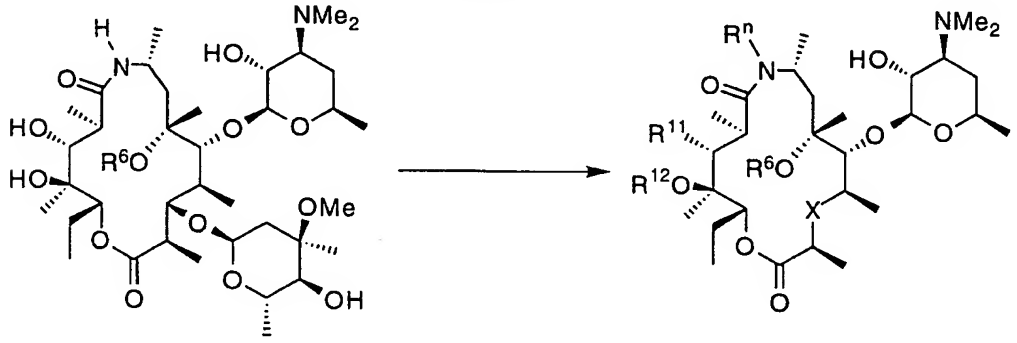
#	Z	X	Rn	R6	Ar
22	C=N(CH2)3Ar	CH2	CH3	H	
23	P(O)O(CH2)3Ar	CH2	CH3	H	
24	P(O)NH(CH2)3Ar	CH2	CH3	H	

Numbering of the 8a-azalides described herein is in accordance with the following scheme.



The compounds of the present invention are prepared from 8a-aza-8a-homo-erythromycin A by a variety of synthetic routes. The process is illustrated by the following generic scheme:

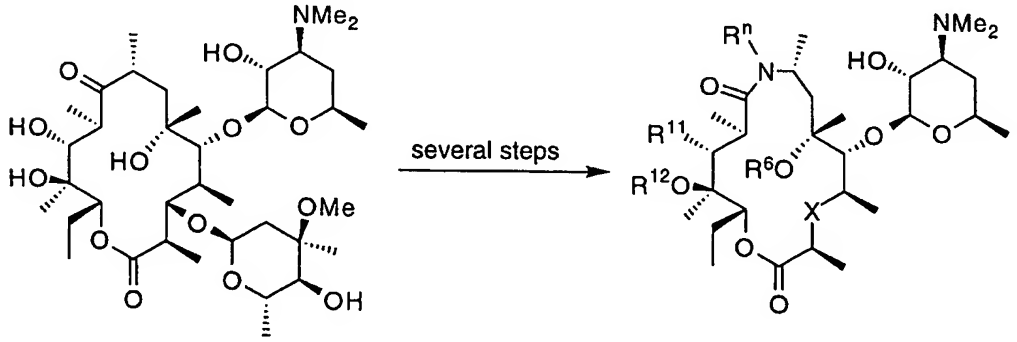
Scheme A



With reference to Scheme A, X, R^6, R^n, R^{11}, and R^{12}, are as defined with respect to the compounds of formula I.

Since 8a-aza-8a-homo-erythromycin A is prepared from erythromycin, the compounds of the present invention are ultimately derived from erythromycin as shown in Scheme B. It will be further recognized that the the compounds of the present invention can be prepared from erythromycin without proceeding through the azalide intermediate shown above by simply altering the order of the steps described herein for the conversion of that intermediate to the compounds of the present invention and the steps required to introduce the 8a nitrogen.

Scheme B



At some point during the synthetic sequence, it is necessary to remove the cladinose attached at C-3 of the starting azalide. Depending on the exact nature of the final synthetic target, the cladinose removal may be best effected at either an early or late stage of the synthesis. This is generally accomplished by treating the macrolide with acid in either aqueous or alcoholic solution. Thus, a solution of the macrolide in an alcohol such as methanol, ethanol, or the like containing from 0.5 to 5% of a strong acid such as hydrochloric acid, sulfuric acid, or the like is stirred for 1 to 36 hours at a temperature ranging from 0°C to 30°C. Alternatively, a solution of the macrolide in a 0.1N to 1 N aqueous solution of a strong acid such as hydrochloric acid, sulfuric acid, or the like is stirred for 1 to 36 hours at a temperature ranging from about 0°C to 30°C. The reaction is worked up and the product macrolide isolated by first making the reaction mixture basic by adding an aqueous solution of a base such as sodium hydroxide, sodium bicarbonate, potassium carbonate and the like then extracting the macrolide product with a suitable organic solvent such as chloroform, ethyl acetate, and the like. If the reaction is run in an alcoholic solvent, the extraction procedure may be improved by first concentrating the reaction mixture under vacuum, preferably after addition of aqueous base to neutralize the acid. When working in the erythromycin series (ketone at C-9, free OH group at C-6), the C-9 ketone must be protected (e.g. as an oxime) before attempting to remove the cladinose under the acidic conditions described above. In the azalide no protection of the amide at C-9 is necessary.

During alkylation of the C-3, 6, 11, or 12 hydroxyl group, it is necessary to protect the nitrogen at C-3' in order to prevent quaternization of the nitrogen. This can be accomplished by protection of the desosamine as the 2',3'-bis-CBZ derivative by using standard macrolide chemistry techniques. Alternatively, the 3'-nitrogen atom can be protected as an arylsulfonamide by N-demethylation followed by sulfonylation with an appropriate sulfonyl halide or sulfonic anhydride. It is not generally necessary to protect the 8a-nitrogen during alkylation reactions. However, protection of the 8a-nitrogen may be useful since it

can alter the order of reactivity of the various hydroxyl groups to alkylation.

Some reactions, including but not limited to alkylation reactions, may also necessitate protection of other hydroxyl groups. This may be accomplished by protection as a silyl ether, an ester, a mixed carbonate, or any of a variety of hydroxyl protecting groups well-known to those skilled in the art.

Alkylation of the C-3, 6, 11, or 12 hydroxyl group may be accomplished by treating a solution of a suitably protected macrolide in a suitable solvent such as dimethylformamide, tetrahydrofuran, and the like with a strong base such as sodium hydride, potassium hexamethyldisilazide, and the like at a temperature ranging from -40°C to 25°C for 1 to 30 minutes then adding a suitable alkylating reagent such as an alkyl iodide, an alkyl bromide, an alkyl trifluoromethane-sulfonate, and epoxide, and the like and stirring the resulting reaction mixture at a temperature ranging from -40°C to 45°C for 15 minutes to 4 hours (appropriate temperature and length of time depends on the exact nature of the alkylating reagent).

Many of the compounds of the present invention contain fewer oxygen atoms attached to the macrolide ring than are present in erythromycin. Such deoxy analogs can be prepared by employing one of many deoxygenation methods for reductive removal of a hydroxyl group. For example, the hydroxyl group can be converted to a xanthate ester by reaction with a base such as sodium hydride, potassium hexa-methyldisilazide, and the like in a solution of a suitable solvent such as tetrahydrofuran, ether, dioxane and the like at temperatures ranging from -20°C to 30°C for 1 to 30 minutes followed by reaction of the resulting alkoxide with excess carbon disulfide and iodomethane to form a methyl xanthate. The methyl xanthate can be purified using standard techniques or, alternatively, may be subjected to the radical deoxygenation procedure without purification. A solution of the methyl xanthate in a suitable solvent such as toluene, benzene, and the like is treated with a radical initiator such as azobis-isobutyrylnitrile (AIBN), triethyl-

borane, and the like and an excess of a hydride source such as tributyltin hydride, triphenyltin hydride, and the like at a temperature ranging from room temperature to 125°C for 1 to 24 hours. The reaction is worked up and the product macrolide isolated using standard macrolide chemistry techniques.

Introduction of the 3-keto group is accomplished by oxidation of a suitably protected precursor with a hydroxyl group at C-3 using one of the many methods for oxidation of secondary alcohols which are well-known to those skilled in the art. For example, a solution of the 3-hydroxy precursor compound in a suitable solvent such as dichloromethane, chloroform, dichloroethane and the like is treated with from 0.95 to 2 molar equivalents of an oxidation reagent such as pyridinium chlorochromate, pyridinium dichromate, Dess-Martin periodinane, chromic acid and the like for 0.1 to 24 hours at a temperature ranging from -40°C to 40°C. The reaction is worked up and the product macrolide isolated by simply filtering the reaction mixture through a piece of filter paper or through a plug of silica gel and evaporating the filtrate under vacuum. Alternatively, the reaction may be worked up by adding an aqueous solution of a base such as sodium hydroxide, sodium bicarbonate, potassium carbonate and the like then extracting the macrolide product with a suitable organic solvent such as chloroform, ethyl acetate, and the like. Evaporation of the organic extract under vacuum then affords the product. Alternatively, oxidation procedures commonly referred to by those skilled in the art as Moffat or Swern oxidations, which involve the use of activated DMSO reagents, may be employed for the oxidation of a 3-hyroxyl group to a 3-ketone. Oxidation using the Dess-Martin periodinane is preferred.

In compounds containing a cyclic carbamate moiety at C-11 and C-12 of the macrolide ring, the cyclic carbamate may be introduced into the erythromycin molecule before the ring expansion and incorporation of the 8a-nitrogen using standard techniques of macrolide chemistry which have been published in the literature and are well known to those skilled in the art. Once the cyclic carbamate moiety is in place, the 8a-nitrogen may be installed using the standard

ring expansion techniques which have been previously published. For compounds containing an alkyl group appended to the nitrogen of the 11,12-cyclic carbamate, the alkyl group may either be incorporated during the construction of the cyclic carbamate or may be added to the completed cyclic carbamate via an alkylation procedure.

Alternatively, the 11,12-cyclic carbamate can be introduced after the 8a-nitrogen has been introduced.

The synthesis of the target compound is completed by removing any protecting groups which are present in the penultimate intermediate using standard techniques which are well known to those skilled in the art. The deprotected final product is then purified, as necessary, using standard techniques such as silica gel chromatography, HPLC on silica gel or on reverse phase silica gel, and the like or by recrystallization.

The final product may be characterized structurally by standard techniques such as NMR, IR, MS and UV. For ease of handling, the final product, if not crystalline, may be lyophilized from, e.g., benzene, tert-butanol and the like, to afford an amorphous, easily handled solid.

The compounds are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts include conventional non-toxic salts or quarternary ammonium salts formed, e.g., from non-toxic inorganic or organic acids. Non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic,

sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The compounds of this invention may be used in a variety of pharmaceutical preparations. They may be employed in powder or crystalline form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically, orally and parenterally by injection.

Oral compositions may take such forms as tablets, capsules, oral suspensions and oral solutions. The oral compositions may utilize conventional formulating agents, and may include sustained release properties as well as rapid delivery forms. The preferred pharmaceutical composition is a table, capsule, suspension or solution, which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated, the route and frequency of administration, the sensitivity of the pathogen to the particular compound selected, the virulence of the infection and other factors. Such matters are left to the routine discretion of the physician according to principles of treatment well known in the antibacterial arts.

The compositions for human delivery per unit dosage, whether liquid or solid, may contain from about 0.01% to as high as about 99% of active material, the preferred range being from about

10-60%. The composition will generally contain from about 15 mg to about 2.5 g of the active ingredient; however, in general, it is preferable to employ a dosage amount in the range of from about 25 mg to 1000 mg.

The preferred method of administration is oral.

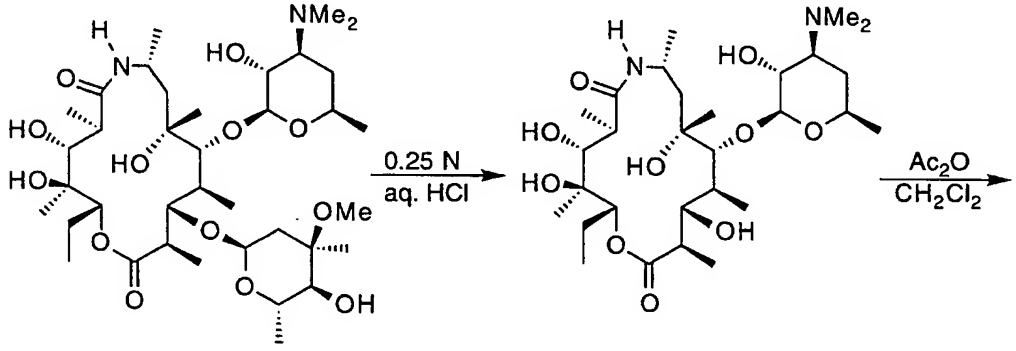
For adults, about 5-50 mg of the compound per kg of body weight given one to four times daily is preferred. The preferred dosage is 250 mg to 1000 mg of the compound given one to four times per day. More specifically, for mild infections a dose of about 250 mg two or three times daily is recommended.

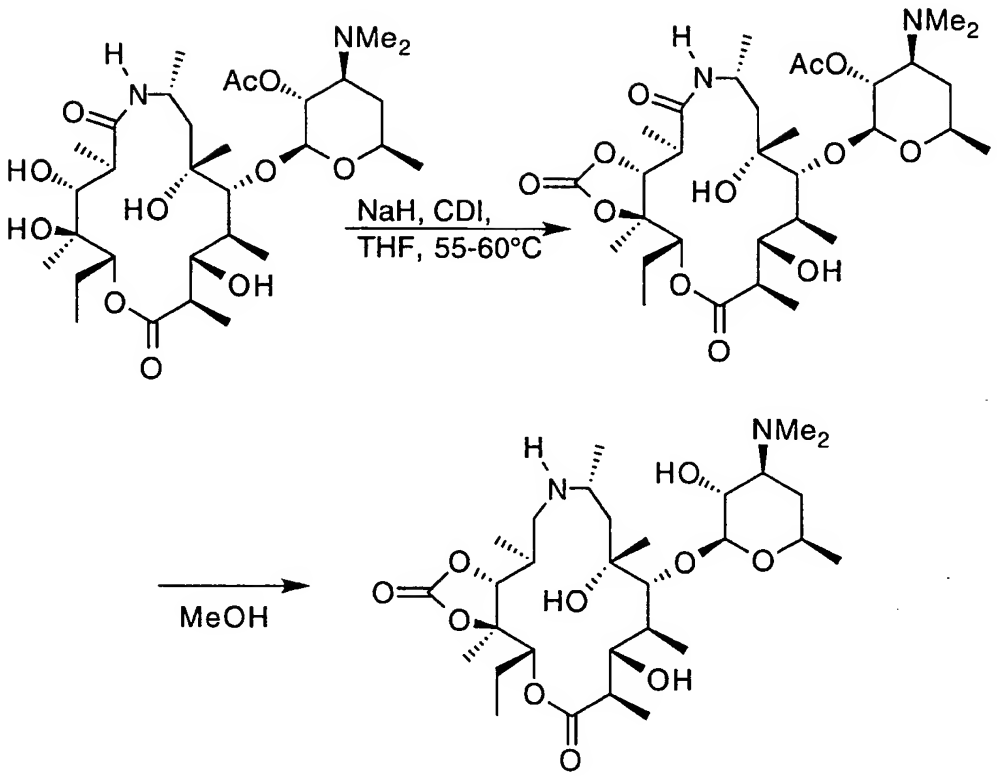
For severe infections caused by organisms at the upper limits of sensitivity to the antibiotic, a dose of about 1000-2000 mg three to four times daily may be recommended.

For children, a dose of about 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg may be recommended.

EXAMPLE 1

8a-aza-3-descladinosyl-8a-homoerythromycin A-11,12-carbonate





Step 1: 8a-aza-3-descladinosyl-8a-homoerythromycin A

A solution of 8a-aza-8a-homoerythromycin A (2.0 g, 2.67 mmol) in 0.25N aqueous hydrochloric acid (100 mL) is stirred at room temperature for 24 hours. The solution is washed with chloroform (2 x 60 mL). The pH of the combined aqueous layers is adjusted to approximately 10 by dropwise addition of 5N aqueous sodium hydroxide. The cloudy aqueous layer is extracted with chloroform (3 x 60 mL). The combined organic extracts are dried over anhydrous potassium carbonate, filtered, and evaporated to give the title compound as a white solid which is used without further purification.

Step 2: 2'-O-Acetyl-8a-aza-3-descladinosyl-8a-homoerythromycin A

A solution of 8a-aza-3-descladinosyl-8a-homoerythromycin A (2.67 mmol) in dichloromethane (30 mL) stirred under a nitrogen

atmosphere as acetic anhydride (0.54 mL, 5.7 mmol) is added. After stirring for 3 hours at room temperature, the solvent is removed *in vacuo*. The residual white foam is dissolved in water (50 mL) and the pH is adjusted to between 10-11 with 5N aqueous sodium hydroxide. The aqueous layer is extracted with dichloromethane (3 x 60 mL). The combined organic extracts are dried (anhydrous sodium sulfate), filtered, and evaporated to give the title compound.

Step 3: 2'-O-Acetyl-8a-aza-3-descladinosyl-8a-homoerythromycin A 11,12-carbonate

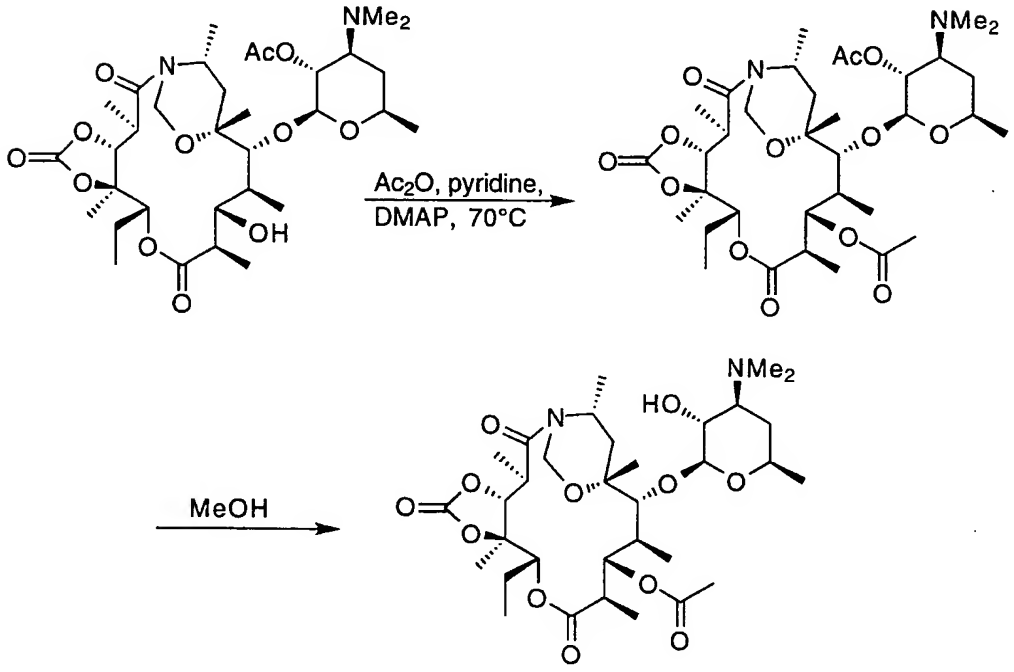
A solution of 2'-O-acetyl-8a-aza-3-descladinosyl-8a-homoerythromycin A (100 mg, 0.16 mmol) in anhydrous tetrahydrofuran (0.53 mL) is stirred at room temperature as sodium hydride (60% dispersion in mineral oil, 13.3 mg, 0.33 mmol) and 1,1'-carbonyldiimidazole (120.4 mg, 0.74 mmol) are added. The resulting mixture is stirred at 55-60°C for 80 minutes. The reaction is partitioned between ethyl acetate and water. The aqueous layer is extracted twice with ethyl acetate. The combined organic layers are washed with brine, dried (anhydrous sodium sulfate), and evaporated to give a yellow solid. The crude solid is purified on a silica gel column (12 g, 2.75 cm dia.) eluted with 1:1 hexane:acetone. The fractions containing product are combined and evaporated to give the title compound.

Step 4: 8a-aza-3-descladinosyl-8a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-8a-aza-3-descladinosyl-8a-homoerythromycin A 11,12-carbonate (15 mg, 0.023 mmol) in methanol (10 mL) is stirred overnight at room temperature then concentrated under vacuum. The resulting oil is dissolved in benzene (3 mL) and lyophilized to give the title compound as a white solid.

EXAMPLE 2

3-O-Acetyl-8a-aza-8a,6-O-methylene-3-descladinosyl-8a-homoerythromycin A 11,12-carbonate



Step 1: 2',3-bis-(O-Acetyl)-8a-aza-8a,6-O-methylene-3-descladinosyl-8a-homoerythromycin A 11,12-carbonate

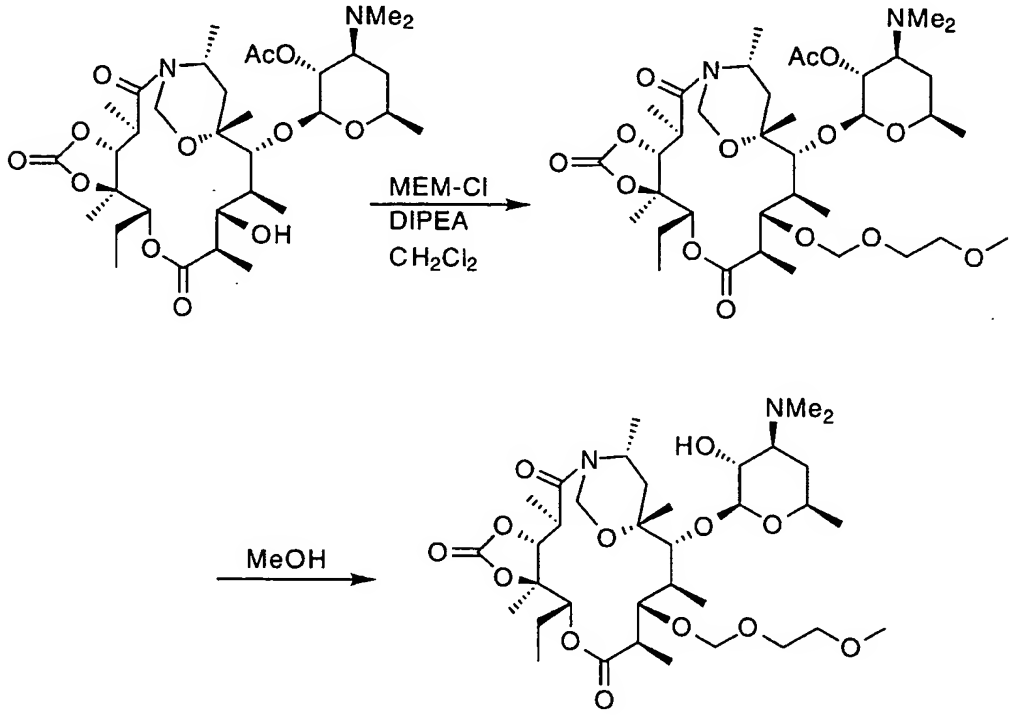
A solution of 2'-O-acetyl-8a-aza-8a,6-O-methylene-3-descladinosyl-11-O,12-O-carbonyl-8a-homoerythromycin A (32.8 mg, 0.05 mmol) in pyridine (1 mL) is stirred at room temperature as acetic anhydride (0.050 mL, 0.53 mmol) is added. The resulting solution is capped and stirred overnight. Additional 4-Dimethylaminopyridine (3.8 mg, 0.031 mmol) and acetic anhydride (0.050 mL, 0.53 mmol) are added and the resulting solution is stirred at 70°C for 4 hours. The reaction mixture is then cooled to room temperature and concentrated. The residue is purified by column chromatography on silica gel (eluted with 1:1 hexane:acetone) to give the title compound.

Step 2: 3-O-Acetyl-8a-aza-8a,6-O-methylene-3-descladinosyl-8a-homoerythromycin A 11,12-carbonate

A solution of 2',3-bis(O-acetyl)-8a-aza-8a,6-O-methylene-3-descladinosyl-8a-homoerythromycin A 11,12-carbonate (28 mg, 0.039 mmol) in methanol (5 mL) is stirred for 24 h then concentrated under vacuum. The resulting oil is dissolved in benzene and lyophilized to give the title compound.

EXAMPLE 3

8a-aza-8a,6-O-methylene-3-descladinosyl-3-O-methoxyethoxymethyl-8a-homoerythromycin A 11,12-carbonate



Step 1: 2'-O-Acetyl-8a-aza-8a,6-O-methylene-3- descladinosyl-3-O-methoxyethoxymethyl-8a- homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-8a-aza-8a,6-O-methylene-3-descladinosyl-8a-homoerythromycin A 11,12-carbonate (100 mg, 0.15 mmol) and N,N-diisopropylethylamine (0.133 mL, 0.76 mmol) in dichloromethane (0.5 mL) is stirred under a nitrogen atmosphere as 2-methoxyethoxymethyl chloride (0.087 mL, 0.76 mmol) is added dropwise. After stirring overnight at room temperature, additional N,N-diisopropylethylamine (0.135 mL, 0.053 mL, & 0.135 mL) and 2-methoxyethoxymethyl chloride (0.087 mL, 0.035 mL, & 0.086 mL) are added to the reaction in three portions over 8 hours. Dichloromethane (2 mL) is also added during this time to facilitate stirring. After stirring overnight, the reaction is partitioned between water and

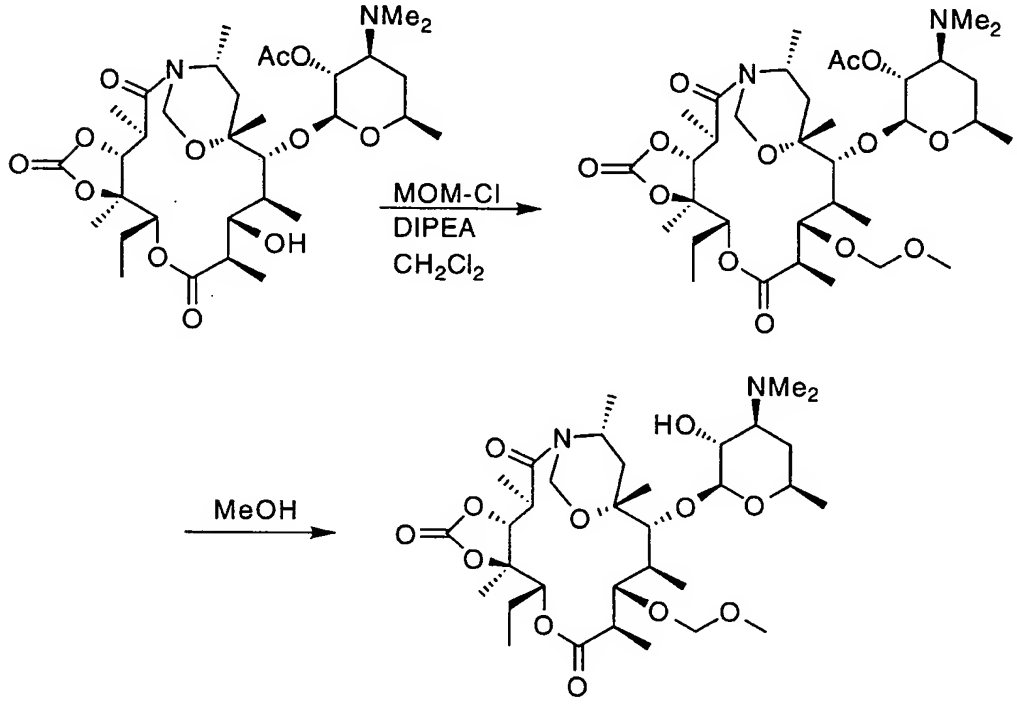
dichloromethane. The aqueous layer is extracted with dichloromethane and the combined organic layers are dried over anhydrous sodium sulfate. The crude product (dissolved in 1:1 hexane:acetone) is loaded onto a silica gel column (30 g, 2.75 cm dia.) and eluted with 1:1 hexane:acetone to give the title compound.

Step 2: 8a-aza-8a,6-O-methylene-3-descladinosyl-3-O-methoxyethoxymethyl-8a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-8a-aza-8a,6-O-methylene-3-descladinosyl-3-O-methoxyethoxymethyl-8a-homoerythromycin A 11,12-carbonate (27 mg, 0.036 mmol) is stirred in methanol overnight at room temperature. The reaction is concentrated and lyophilized (from benzene) to give the title compound.

EXAMPLE 4

8a-aza-8a,6-O-methylene-3-descladinosyl-3-O-methoxymethyl-8a-homoerythromycin A-11,12-carbonate



Step 1: 2'-O-Acetyl-8a-aza-8a,6-O-methylene-3- descladinosyl-3-O-methoxymethyl-8a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-8a-aza-8a,6-O-methylene-3-descladinosyl-8a-homoerythromycin A 11,12-carbonate (31.5 mg, 0.048 mmol) and N,N-diisopropylethylamine (0.046 mL, 0.264 mmol) in dichloromethane (1 mL) is stirred at room temperature as chloromethyl methyl ether (0.018 mL, 0.24 mmol) is added. The solution is stirred at room temperature for 20 hours. Then additional quantities of N,N-diisopropylethyl-amine (0.046 mL, 0.046 mL, 0.092 mL, & 0.092 mL) and chloro-methyl methyl ether (0.018 mL, 0.018 mL, 0.036 mL, & 0.036 mL) are added portionwise. The reaction is then partitioned between saturated aqueous potassium carbonate and dichloromethane. The organic layer is dried (anhydrous

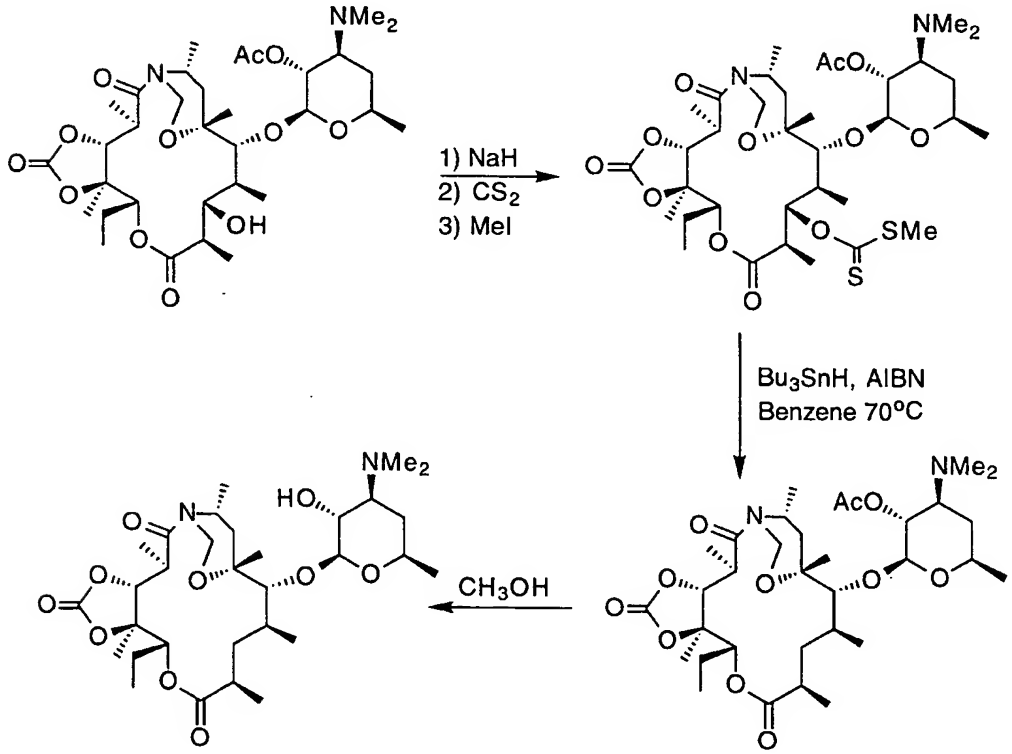
potassium carbonate), filtered, and concentrated. The crude product is chromatographed on a silica gel column to give the title compound.

Step 2: 2'-O-Acetyl-8a-aza-8a,6-O-methylene-3- descladinosyl-3-O-methoxymethyl-8a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-8a-aza-8a,6-O-methylene-3-descladinosyl-3-O-methoxymethyl-8a-homoerythromycin A 11,12-carbonate (9.0 mg, 0.0126 mmol) in methanol (3 mL) is stirred for 20 hours at room temperature. The reaction is concentrated and the residue is lyophilized from benzene to give the title compound.

EXAMPLE 5

Synthesis of 3-descladinosyl-3-deoxy-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate



Step 1: 2'-O-Acetyl-3-descladinosyl-3-O-methylxanthyl-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate

Sodium hydride (166 mg of 60% oil dispersion, 4.14 mmol) is added to a cold (-20°C) solution of 2'-O-Acetyl-3-descladinosyl-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate (905 mg, 1.38 mmol) in anhydrous DMF (11 mL). The reaction mixture is stirred for 15 minutes at -20°C then carbon disulfide (0.124 mL, 2.09 mmol) is added. The mixture is stirred for 15 minutes at -20°C then iodomethane (0.129 mL, 2.09 mmol) is added and the bath is allowed to warm up. When the bath has warmed to -10°C, after about 40 minutes, the flask is removed and stirred at room temperature. The mixture is stirred at room temperature for 2 hours. The reaction mixture is then poured into ethyl acetate. The organic layer is washed 4 times with saturated aqueous $NaHCO_3$, dried over K_2CO_3, and filtered. Removal of solvent under reduced pressure affords crude product.

Step 2: 2'-O-Acetyl-3-descladinosyl-3-deoxy-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate

The product of step 1 and 23 mg of AIBN (0.14 eq) are dissolved in 20 mL benzene and stirred at 90°C. To this, 1.10 mL of Bu_3SnH is added and the reaction is heated at reflux for 4 hours. The reaction is cooled to room temperature and solvent is removed under reduced pressure. The crude material is purified by silica chromatography eluting with 2:1 hexane:acetone. The fractions containing the desired material are combined and solvent removed under reduced pressure to yield the title compound.

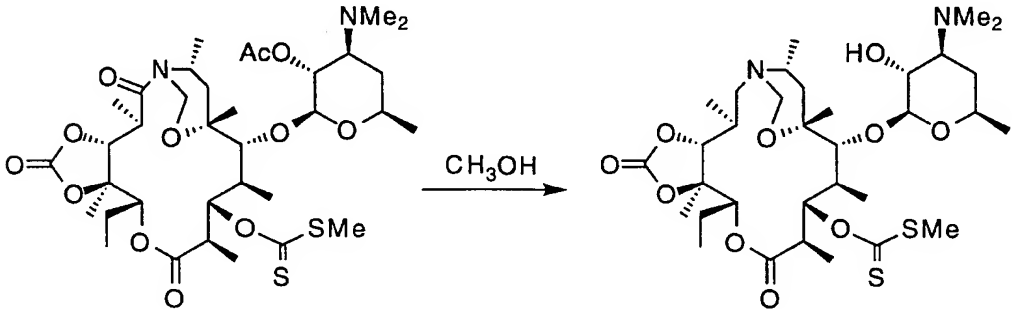
Step 3: 3-descladinosyl-3-deoxy-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-Acetyl-3-descladinosyl-3-deoxy-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate (537 mg) in methanol (30 mL) is stirred at room temperature overnight. The solvent is removed under reduced pressure to afford

crude product which is purified by silica chromatography eluted with 1:1 hexane: acetone to afford the title compound.

EXAMPLE 6

3-descladinosyl-3-O-methylxanthyl-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate

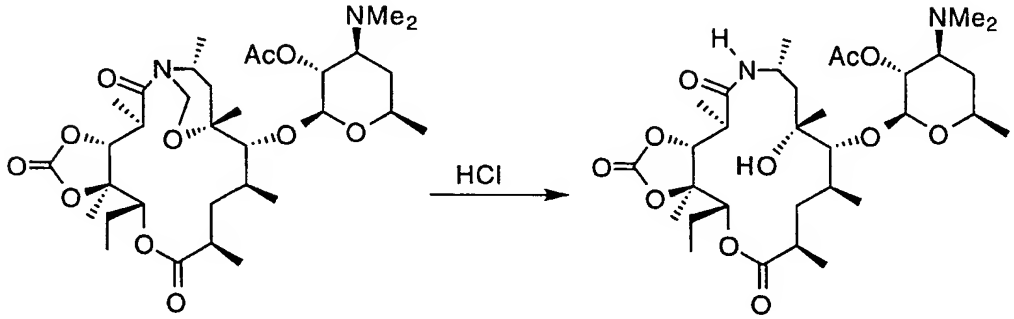


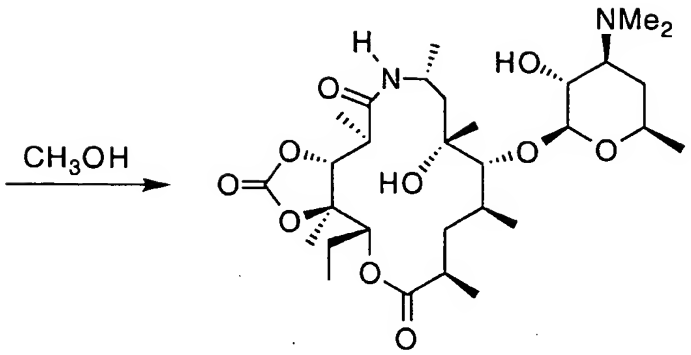
Step 1: 3-descladinosyl-3-O-methylxanthyl-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-Acetyl-3-O-methylxanthyl-3-deoxy-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate (11 mg) in methanol (4 mL) is stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue is lyophilized from benzene to afford the title compound.

EXAMPLE 7

Synthesis of 3-descladinosyl-3-deoxy-8a-aza-8a-homoerythromycin A 11,12-carbonate





Step 1: 2'-O-Acetyl-3-descladinosyl-3-deoxy-8a-aza-8a-homoerythromycin A 11,12-carbonate

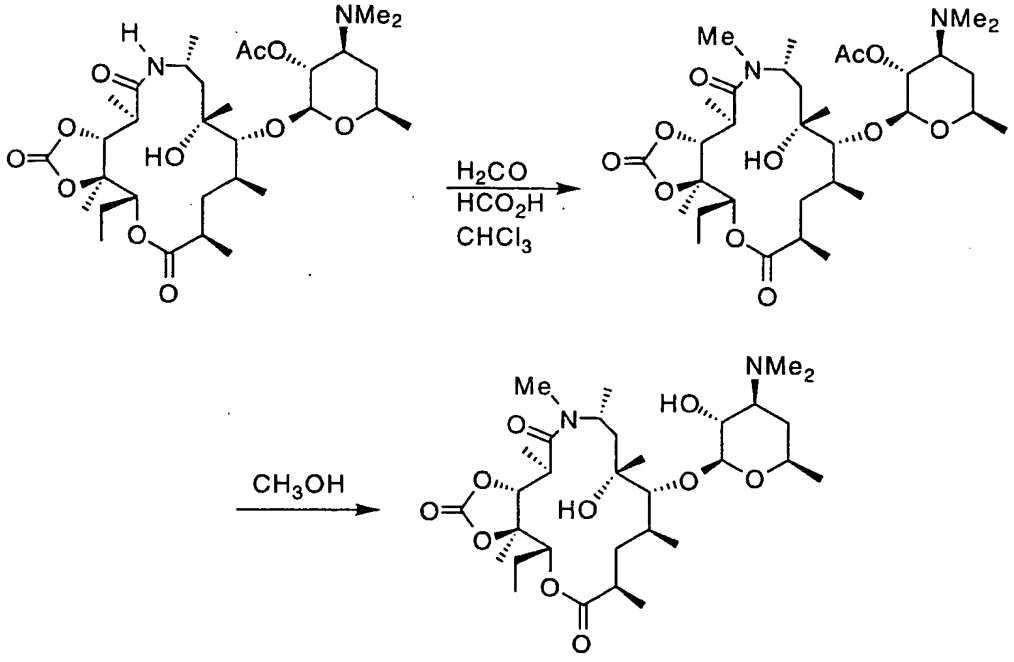
A solution of 2'-O-Acetyl-3-descladinosyl-3-deoxy-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate (20.0 mg, 0.031 mmol) in 1 ml 0.25 M HCl is stirred at room temperature for 3 hours. The mixture is added to $CHCl_3$, neutralized with sat. aq. K_2CO_3 and extracted with $CHCl_3$. The combined organic layers are washed with sat. aq. K_2CO_3, dried over anhydrous K_2CO_3, filtered, and evaporated to afford the title compound.

Step 2: 3-descladinosyl-3-deoxy-8a-aza-8a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-Acetyl-3-descladinosyl-3-deoxy-8a-aza-8a-homoerythromycin A 11,12-carbonate (9.4 mg) in methanol (2 mL) is stirred at room temperature overnight. The solvent is removed under reduced pressure and the crude product is purified by chromatography on a silica gel column eluted with 1:1 (90:10:1 CH_2Cl_2:CH_3OH:methanolic NH_3):CH_2Cl_2 to yield the title compound.

EXAMPLE 8

Synthesis of 3-descladinosyl-3-deoxy-8a-aza-8a-methyl-8a-homoerythromycin A 11,12-carbonate



Step 1: 2'-O-Acetyl-3-descladinosyl-3-deoxy-8a-aza-8a-methyl-8a-homoerythromycin A 11,12-carbonate

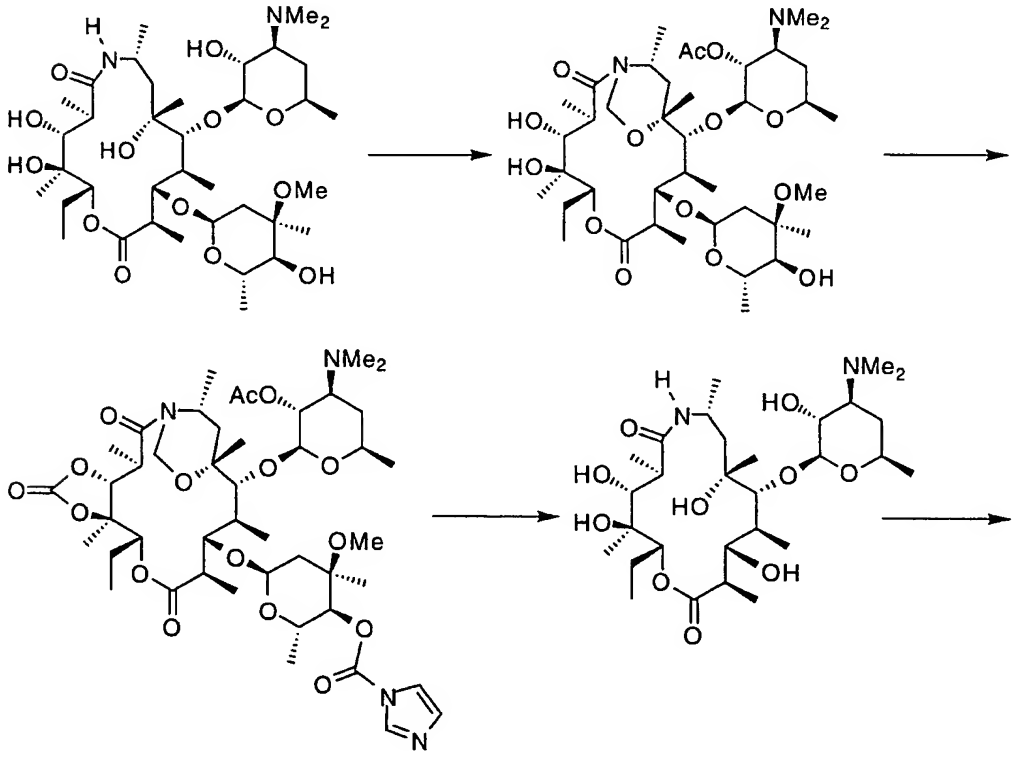
Formaldehyde (0.0080 mL, 0.109 mmol) and formic acid (0.0090 mL, 0.212 mmol) are added to a solution of 2'-O-Acetyl-3-descladinosyl-3-deoxy-8a-aza-8a-homoerythromycin A 11,12-carbonate (64 mg, 0.101 mmol) in chloroform (1 mL). The reaction mixture is stirred at 60°C for 2 days then diluted with dichloromethane and water. The pH is adjusted to 4-5 with glacial acetic acid. The organic layer is separated and the aqueous layer is extracted twice with dichloromethane. The combined organic layers are washed and dried over anhydrous K_2CO_3, filtered, and evaporated to afford the title compound.

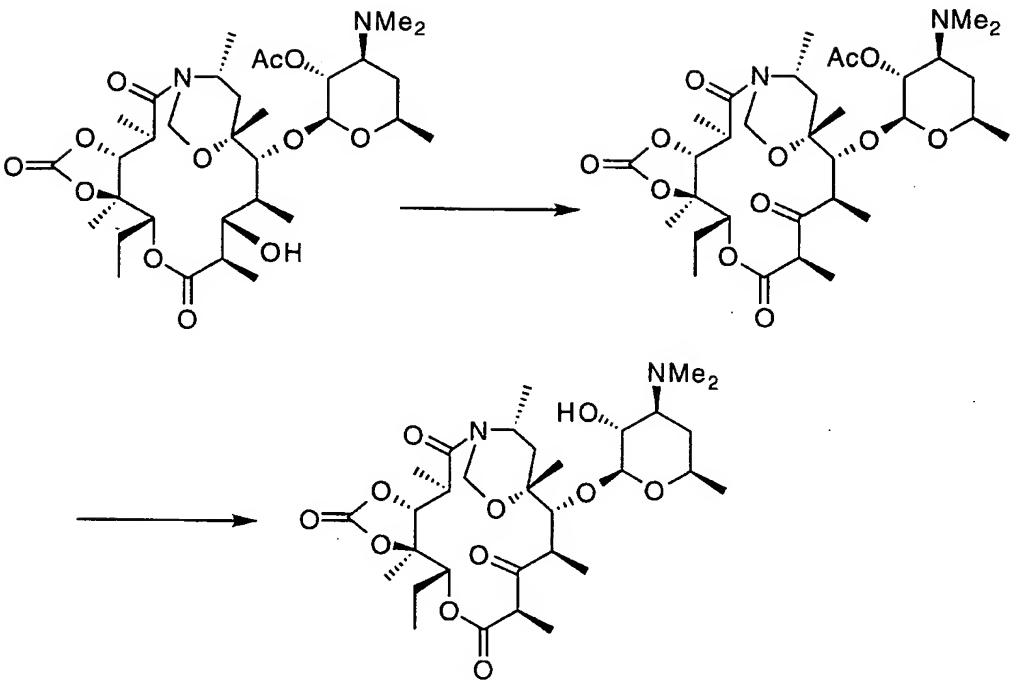
Step 2: 3-descladinosyl-3-deoxy-8a-aza-8a-methyl-8a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-Acetyl-3-descladinosyl-3-deoxy-8a-aza-8a-methyl-8a-homoerythromycin A 11,12-carbonate (62 mg, 0.096 mmol) in methanol (5 mL) is stirred at room temperature overnight. The solvent is removed under reduced pressure and the crude product is purified by chromatography on a silica gel column eluted with 1:1 hexane:acetone to yield the title compound.

EXAMPLE 9

3-descladinosyl-3-oxo-8a-aza-8a-N,6-O-methylene-8a-homoerythromycin A 11,12-carbonate





Step 1: 2'-O-Acetyl-8a-N,6-O-methylene-8a-aza-8a-homoerythromycin A

To a solution of 2.98 g of 8a-aza-8a-homoerythromycin A in 70 mL of chloroform is added 0.750 mL of 37% aq. formaldehyde. The mixture is refluxed for 1.5 hours, after which time the reaction is diluted with 150 mL chloroform and extracted with 50 mL of sat. aq. potassium carbonate. The organic layer is separated, dried over anhydrous potassium carbonate, and the solvent is removed under reduced pressure. The crude residue is dissolved in 20 mL of 1:1 ethyl acetate:methylene chloride, 0.800 mL of acetic anhydride is added, and the mixture is stirred at room temperature for 1.5 hours. The solvent is removed under reduced pressure to afford the title compound.

Step 2: 2'-O-Acetyl-8a-N,6-O--methylene-8a-aza-8a-homoerythromycin A-4"-imidazoylcarbamate-11,12 carbonate

To a solution of 0.103 g (0.127 mmol) of 2'-O-Acetyl-8a-N,6-O--methylene-8a-aza-8a-homoerythromycin A in 1.0 mL of

tetrahydrofuran is added 0.103 g of carbonyldiimidazole (5 eq.), then 12.7 mg of sodium hydride (60% oil dispersion). The mixture is refluxed for 25 minutes, after which time the reaction is diluted with 50 mL ethyl acetate and washed three times with 10 mL of sat. aq. sodium bicarbonate. The organic layer is separated, dried over anhydrous potassium carbonate, and the solvent is removed under reduced pressure to afford the title compound.

Step 3: 2'-O-Acetyl-3-descladinosyl-8a-aza-8a-homoerythromycin A-11,12 carbonate

A solution of 0.110 g (0.127 mmol) of 2'-O-acetyl-8a-N,6-O-methylene-8a-aza-8a-homoerythromycin A-4"-imidazoyl-carbamate-11,12 carbonate in 5.0 mL of 0.25 N aq. HCl is allowed to stir at room temperature for 12 hours, after which time the reaction is diluted with 50 mL ethyl acetate and washed three times with 30 mL of sat. aq. sodium bicarbonate. The organic layer is separated, dried over anhydrous potassium carbonate, and the solvent is removed under reduced pressure to afford the title compound.

Step 4: 2'-O-Acetyl-3-descladinosyl-8a-N,6-O-methylene 8a-aza-8a-homoerythromycin A-11,12 carbonate

To a solution of 0.074 g (0.122 mmol) of 2'-O-Acetyl-3-descladinosyl-8a-aza-8a-homoerythromycin A-11,12 carbonate in 2.0 mL of chloroform is added 0.050 mL of 37% aq. formaldehyde. The mixture is refluxed for 1 hour, after which time the reaction is diluted with 150 mL chloroform and extracted with 50 mL of sat. aq. potassium carbonate. The organic layer is separated, dried over anhydrous potassium carbonate, and the solvent is removed under reduced pressure to afford the title compound.

Step 5: 2'-Acetoxy-3-descladinosyl-3-oxo-8a-N,6-O-methylene-8a-aza-8a-homoerythromycin A-11,12 carbonate

To a solution of 0.158 g of 2'-O-Acetyl-3-descladinosyl-

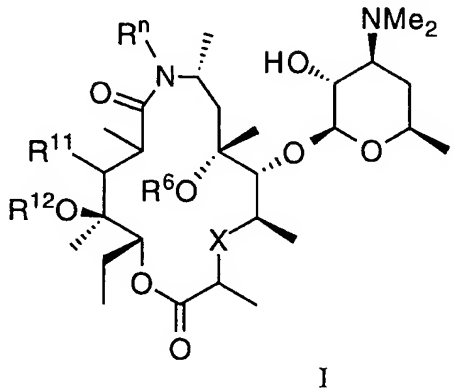
8a-N,6-O-methylene-8a-aza-8a-homoerythromycin A-11,12 carbonate in 1.6 mL of chloroform is added 158 mg of the Dess-Martin periodinane reagent. The mixture is stirred at room temperature for 35 minutes, after which time the reaction is diluted with 30 mL chloroform and 30 mL of saturated aqueous sodium bicarbonate. The organic layer is separated and the aqueous layer is back extracted with 15 mL of methylene chloride. The combined organics are dried over anhydrous potassium carbonate, and the solvent is removed under reduced pressure. The crude material is chromatographed on silica gel eluted with 1:1 hexane:acetone. The fractions containing the desired product are combined and evaporated to afford the title compound.

Step 6: 3-descladinosyl-3-oxo-8a-N,6-O-methylene-8a-aza-8a-homoerythromycin A-11,12 carbonate

A solution of 0.035 g of 2'-O-acetyl-3-descladinosyl-3-oxo-8a-N,6-O-methylene-8a-aza-8a-homoerythromycin A-11,12 carbonate in 2.0 mL of methanol is stirred at room temperature for 5.5 hours, after which time the solvent is removed under reduced pressure. The crude material is chromatographed on silica gel eluting with 1:4 hexane:acetone. The fractions containing the desired product are combined and evaporated to afford the title compound.

WHAT IS CLAIMED IS:

1. A compound represented by formula I:



I

or a salt or hydrate thereof wherein:

X represents CH_2, CHF, CF_2, $C=CH_2$, CHSR, $CHCH_3$, C=S, C=O, C=NOR, CHNR'R" or CHOR;

R represents H, C_{1-6} alkyl, CS_2CH_3 or phenyl, said C_{1-6} alkyl being uninterrupted or interrupted by O, $S(O)_y$ wherein y is 0, 1 or 2, NH or C(O), and being unsubstituted or substituted with 1-3 R^a groups, as defined below;

R^n represents H, C_{1-6} alkyl or $-(CH_2)_nAr$ wherein n represents an integer of from 1 to 10, said C_{1-6} alkyl chain and $-(CH_2)_n$ being uninterrupted or interrupted by 1-3 of O, $S(O)_y$, NH, NCH_3 or C(O) wherein y is as previously defined, and being unsubstituted or substituted with 1-3 R^a groups as defined below,

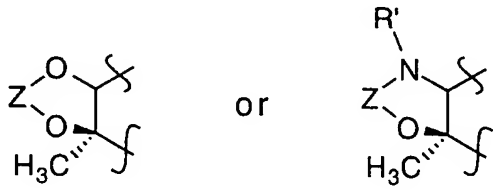
or R^n is taken in conjunction with R^6 as defined below;

Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 groups R^a which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, phenyl and pyridyl and when two substituent groups are attached to Ar, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, containing from 0-2 heteroatoms as defined above;

R^{11} is selected from the group consisting of: OH, NR'R", $O(CH_2)_nAr$ and $S(CH_2)_nAr$, wherein $(CH_2)_n$ and Ar are as previously defined;

R^{12} is selected from the group consisting of: H, C_{1-6} alkyl and $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as previously defined;

or R^{11} and R^{12} taken together with the intervening atoms form an additional ring of the following structure:



wherein :

R' is selected from H, C_{1-3} alkyl, NHR"and $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as previously defined;

R" represents H, C_{1-3} alkyl or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined above;

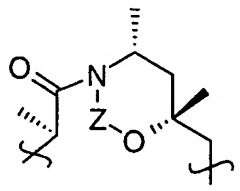
Z represents CH_2, C(O), C(NR"), P(O)OR", $P(O)NR^nR"$, $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 wherein R" and X are as defined above;

R^z represents C_{1-6} alkyl or phenyl;

R^6 represents H or CH_3; and

R^n is as defined above; or

R^6 and R^n taken together with the intervening atoms form the following structure:



in which Z is as described above.

2. A compound in accordance with claim 1 wherein X represents CH_2, CHF, CF_2.

3. A compound in accordance with claim 1 wherein X represents $C=CH_2$, C=S or CHSR.

4. A compound in accordance with claim 1 wherein X represents C(O) or CHOR.

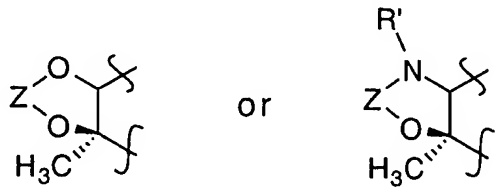
5. A compound in accordance with claim 1 wherein R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$.

6. A compound in accordance with claim 1 wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, phenyl and pyridyl.

7. A compound in accordance with claim 1 wherein R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined.

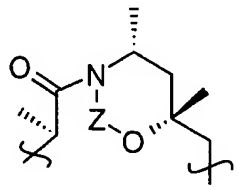
8. A compound in accordance with claim 1 wherein R^{12} represents H, C_{1-6} alkyl or $(CH_2)_n$-Ar.

9. A compound in accordance with claim 1 wherein R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring as shown in the following structure:



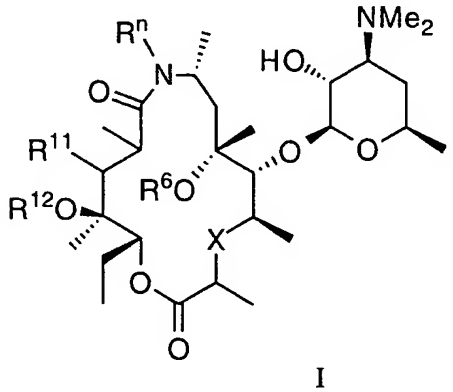
wherein Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 wherein R', R" and X are as originally defined.

10. A compound in accordance with claim 1 wherein R^6 and R^n taken together with the intervening atoms form a ring as shown in the following structure:



in which Z is as described above.

11. A compound represented by formula I:



I

or a salt or hydrate thereof, wherein:

X represents CH_2, CHF or CF_2;

R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$,

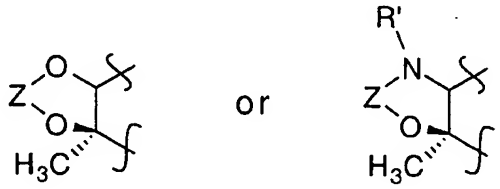
wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl,

phenyl and pyridyl or R^n is taken in conjunction with R^6 as defined below;

R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined;

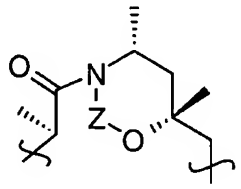
R^{12} represents H, C_{1-6} alkyl or $(CH_2)_n$-Ar;.

or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring of the following structure:



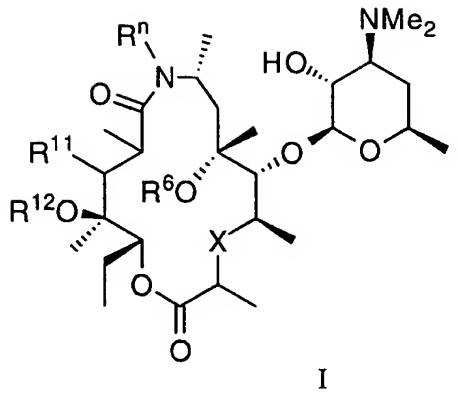
wherein Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 wherein R', R" and X are as originally defined;

R^6 is H or CH_3, or R^6 and R^n taken together with the intervening atoms form the following structure:



in which Z is as described above.

12. A compound represented by formula I:



I

or a salt or hydrate thereof, wherein:

X represents $C=CH_2$, C=S or CHSR;

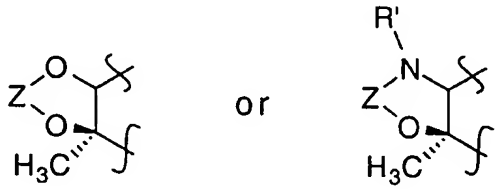
R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$,

wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, phenyl and pyridyl or R^n is taken in conjunction with R^6 as defined below;

R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined;

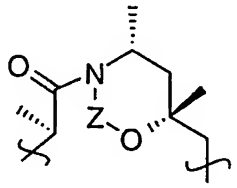
R^{12} represents H, C_{1-6} alkyl or $(CH_2)_n$-Ar;.

or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring of the following structure:



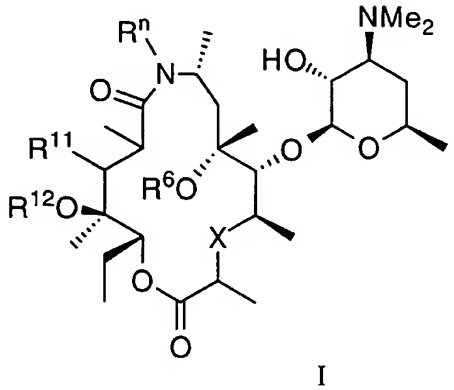
wherein Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 wherein R', R" and X are as originally defined;

R^6 is H or CH_3, or R^6 and R^n taken together with the intervening atoms form the following structure:



in which Z is as described above.

13. A compound represented by formula I:



I

or a salt or hydrate thereof, wherein:

X represents C(O) or CHOR;

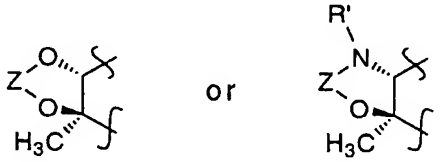
R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$,

wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, phenyl and pyridyl or R^n is taken in conjunction with R^6 as defined below;

R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined;

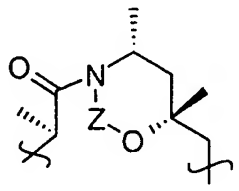
R^{12} represents H, C_{1-6} alkyl or $(CH_2)_n$-Ar;.

or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring of the following structure:



wherein Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 wherein R', R" and X are as originally defined;

R^6 is H or CH_3, or R^6 and R^n taken together with the intervening atoms form the following structure:



in which Z is as described above.

14. A compound in accordance with claim 1 having the name:

8a-aza-8a-methyl-3-descladinosyl-8a-homoerythromycin A-11,12-carbonate;

3-O-Acetyl-8a-aza-8a,6-O-methylene-3-descladinosyl-8a-homoerythromycin A 11,12-carbonate;

8a-aza-8a,6-O-methylene-3-descladinosyl-3-O-methoxyethoxymethyl-8a-homoerythromycin A 11,12-carbonate;

8a-aza-8a,6-O-methylene-3-descladinosyl-3-O-methoxymethyl-8a-homoerythromycin A-11,12-carbonate;

8a-aza-3-descladinosyl-8a-homoerythromycin A 11,12-carbonate-8a-N,6-O-carbamate;

3-descladinosyl-3-oxo-8a-aza-8a-homoerythromycin A 11,12-carbonate-8a-N,-6-O-carbamate ;

3-descladinosyl-3-deoxy-8a-aza-8a-homoerythromycin A-11,12-carbonate-8a-N,-6-O-carbamate;

3-descladinosyl-3-deoxy-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate;

3-descladinosyl-3-O-methylxanthyl-8a-N,-6-O-methylene-8a-aza-8a-homoerythromycin A 11,12-carbonate;

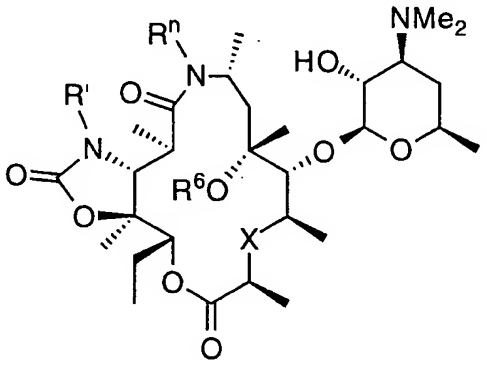
3-descladinosyl-3-deoxy-8a-aza-8a-homoerythromycin A 11,12-carbonate;

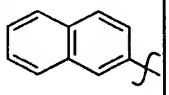
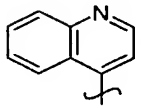
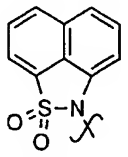
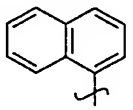
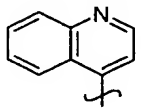
3-descladinosyl-3-deoxy-8a-aza-8a-methyl-8a-homoerythromycin A 11,12-carbonate, or

3-descladinosyl-3-oxo-8a-aza-8a-N,6-O-methylene-8a-homoerythromycin A 11,12-carbonate.

15. A compound having a structure in accordance with one of the following tables:

Table 1



#	X	Rn	R6	R'	Ar
1	CH_2	CH_3	H	$(CH_2)_4Ar$	
2	CH_2	CH_3	H	$(CH_2)_4Ar$	
3	CH_2	CH_3	H	$(CH_2)_4Ar$	
4	CH_2	CH_3	H	$(CH_2)_3Ar$	
5	CHF	CH_3	CH_3	$(CH_2)_4Ar$	
6	CF_2	CH_3	CH_3	$(CH_2)_4Ar$	

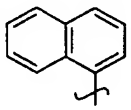
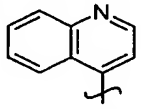
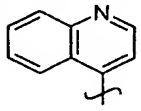
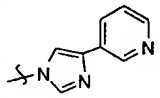
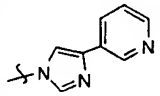
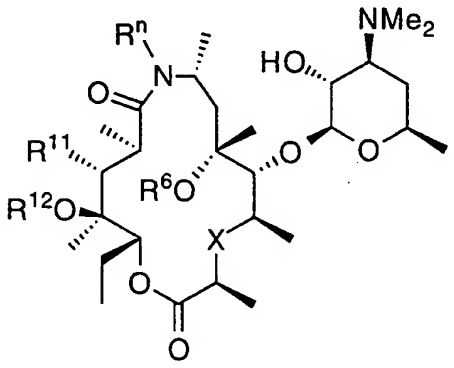
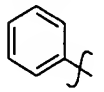
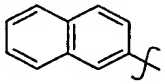
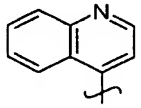
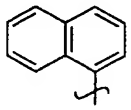
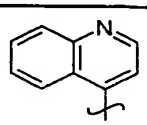
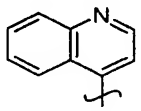
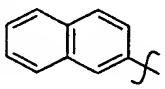
7	CH_2	---CH_2---		$(CH_2)_4Ar$	
8	CH_2	---CH_2---		$NH(CH_2)_3Ar$	
9	C=O	CH_3	CH_3	$NH(CH_2)_3Ar$	
10	C=O	H	CH_3	$(CH_2)_4Ar$	
11	C=O	CH_3	CH_3	$(CH_2)_4Ar$	

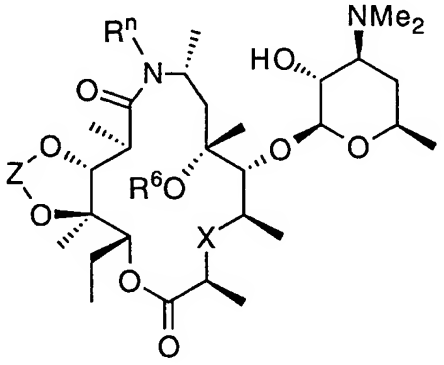
Table 2

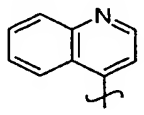
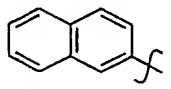
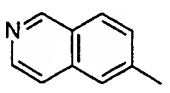


#	X	Rn	R6	R11	R12	Ar
10	CH_2	CH_3	H	$O(CH_2)_3Ar$	H	
11	CH_2	CH_3	H	OH	$(CH_2)_3Ar$	
12	CH_2	CH_3	H	$O(CH_2)_3Ar$	H	
13	CHF	CH_3	CH_3	$O(CH_2)_4Ar$	H	
14	CH_2	CH_3	H	$S(CH_2)_4Ar$	H	
15	CH_2	$(CH_2)_4Ar$	H	OH	H	
16	CH_2	$(CH_2)_4SO_2Ar$	H	OH	H	

17	C=O	CH_3	CH_3	OH	H	------
18	CH_2	--P(O)OCH_3--		OH	H	------
19	C=O	--P(O)OCH_3--		OH	H	------
20	CH_2	--C(O)CH_2--		OH	H	------
21	C=O	--C(O)CH_2--		OH	H	------

Table 3



#	Z	X	Rn	R6	Ar
22	C=N$(CH_2)_3$Ar	CH_2	CH_3	H	
23	P(O)O$(CH_2)_3$Ar	CH_2	CH_3	H	
24	P(O)NH$(CH_2)_3$Ar	CH_2	CH_3	H	

16. A pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

17. A method of treating a bacterial infection in a mammalian patient in need of such treatment which is comprised of administering to said patient a compound of formula I in an amount which is effective for treating a bacterial infection.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/21594

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07D 521/00; C07H 17/08; A61K 31/70
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 540/454, 455, 456, 457; 514/183, 63, 80, 81, 100, 101, 450, 451

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,189,159 A (WILKENING) 23 FEBRUARY 1993, cols. 4-19	1-17
A	US 5,202,434 A (WILKENING) 13 APRIL 1993, cols. 2-19	1-17
A	EP 0 549 040 A1 (MERCK & CO. INC.) 30 JUNE 1993, Pages 2-7.	1-17
A	EP 0 508 699 A1 (MERCK & CO. INC.) 14 OCTOBER 1992, pages 2-35.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 30 NOVEMBER 1998	Date of mailing of the international search report 15 JAN 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BRUCK KIFLE Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/21594

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

540/454, 455, 456, 457; 514/63, 80, 81, 100, 101, 183, 450, 451